Remarks

Claims 1, 3, 11 and 27-33 were pending in the subject application. By this amendment, new dependent Claims 34-37 have been added. Support for new Claims 34-37 can be found in the specification as filed at page 12, line 8. Accordingly, entry of this amendment is respectfully requested.

35 U.S.C. § 102(b) Rejection

Claims 1, 3, 11, 27, 28 and 29-33 were rejected under 35 U.S.C. §102(b) as anticipated by WO 01/64749 ("Kloetzer"). This rejection is respectfully traversed.

Kloetzer describes the use of an MIF antibody for treating arthritis, psoriasis, glomerulonephritis, septic shock, atopic dermatitis, and retinopathy associated with diabetes or lupus. Kloetzer does not teach a method of inhibiting the progression of type 1 diabetes in a mammal having type 1 diabetes, as set forth in Claims 1, 3, 11, 27, 34 and 35, or a method of inhibiting the development of type 1 diabetes in a mammal at risk for type 1 diabetes, as set forth in Claims 29-33, 36 and 37. Diabetic retinopathy is not type 1 diabetes. It is a separate condition (a retinopathy) which can occur in diabetes patients, but does not always occur. It does not necessary follow that a proposed treatment of diabetic retinopathy would necessarily result in inhibiting the progression of type 1 diabetes in a mammal having type 1 diabetes, or in inhibiting the development of type 1 diabetes in a mammal at risk for type 1 diabetes. Nothing in Kloetzer teaches that the treatment of a potential complication of type 1 diabetes such as diabetic retinopathy, would necessarily result in inhibiting the progression or development of the underlying disease.

Accordingly, applicant maintains that the anticipation rejection is improper and respectfully request that the Examiner reconsider and withdraw this rejection.

35 U.S.C. § 103(a) Rejection

Bojunga in view of Nishihira

Claims 1, 3, 11, 27, 28 and 29-33 were rejected under 35 U.S.C. §103(a) as unpatentable over Bojunga et al. ("Bojunga") in view of Nishihira et al. ("Nishihira"). This rejection is respectfully traversed.

Bojunga suggests that MIF may play a possible role in autoimmune-inflammatory events such as type-1 diabetes. In this regard, this potential role was based on preliminary studies in Bojunga in which it was shown that MIF-mRNA expression was elevated in the splenic lymphocytes of NOD mice in which diabetes was spontaneously induced. However, the MIF protein levels in the diabetic animals were less than in the normal controls. In another set of experiments, Bojunga evaluated the effect of MIF-protein treatment on diabetes in the NOD mice. While MIF treatment led to an increase in diabetes incidence over the untreated animals, Bojunga stated that this trend was not statistically significant. In summary, Bojunga suggests that MIF may be involved in diabetes. However, Bojunga does not provide any data which supports that an agent that inhibits a macrophage migration inhibitory factor (MIF) in the mammal, wherein the agent comprises a binding site of an antibody that binds specifically to MIF, would be effective in inhibiting the progression of type 1 diabetes in a mammal having type 1 diabetes or in inhibiting the development of type 1 diabetes in a mammal at risk for type 1 diabetes.

With respect to elevated mRNA expression, this is not necessarily predictive or translate into elevated protein levels. As stated in Greenbaum et al. (Genome Biology 2003, 4:117, copy attached), "while mRNA expression values have shown their usefulness in a broad range of applications, including the diagnosis and classification of cancers [22,23], these results are almost certainly only correlative, rather than causative; in the end it is most probably the concentration of proteins and their interactions that

are the true causative forces in the cell, and it is the corresponding protein quantities that we ought to be studying." It is notable in this regard that Bojunga actually shows *decreased* MIF *protein* levels in mouse lymphocytes of spontaneously diabetic and CY-treated NOD mice and Bojunga merely speculates as to why this might be. This can be considered in light of the statement in Greenbaum et al. that there are "presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their in vivo half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture." (emphasis added).

Applicant further draws the Examiner's attention to Ogata et al., Neuroscience letters, 264(3):173-177 (1998), a copy of which is submitted herewith by EFS, where high expression of MIF mRNA was observed in both neurons and astrocytes, but protein was found in astrocytes only and *not* in the neurons (see, for example, page 176, top paragraph, and see first whole paragraph on page 176 where it is stated the "present results showed that the magnitude of MIF mRNA expression did not correlate with that of MIF protein") (emphasis added).

Based on the teachings of Bojunga, it was not predictable whether MIF protein levels (elevated or decreased, for example) are involved in type 1 diabetes, or the progression of type 1 diabetes. It also was not predictable that inhibiting MIF protein activity (e.g. using an agent that comprises a binding site of an antibody that binds specifically to macrophage migration inhibitory factor (MIF)) would have any effect on type I diabetes based on the *mRNA* data of Bojunga. One skilled in the art would not know that inhibiting MIF protein activity would have any effect on type I diabetes based

on Bojunga showing *decreased* MIF protein levels in lymphocytes of spontaneously diabetic and CY-treated NOD mice. Moreover, it was not predictable that treating MIF protein activity would be efficacious in *inhibiting the progression* of type 1 diabetes based on the mRNA data of Bojunga regarding incidence of diabetes.

In summary, there is no indication in Bojunga that type 1 diabetes can be treated with an agent comprising a binding site of an antibody that binds specifically to MIF, or such an agent could be used to inhibit the development of type 1 diabetes. Firstly, there is no indication that MIF protein levels are elevated in type 1 diabetes, and mRNA levels are not necessarily predictive of MIF protein levels. Secondly, while Bojunga "tested the effect of MIF-protein treatment on diabetes incidence" by administering exogenous MIF protein, no statistically different results were found in diabetes incidence as compared to control (see page 184, right hand side, last whole paragraph). Moreover, Bojunga states "lymphocytic MIF-protein content did not significantly differ between spontaneously diabetic and CY-treated NOD mice" even though the MIF mRNA expression is approximately twofold in the former over the latter (see page 182, right hand side, section 182). Thus, the relationship between MIF mRNA and MIF protein levels is complex. Moreover, while Bojunga states that exogenous MIF protein administration "led to an increase in diabetes incidence" it was not statistically significant, and notably there is no indication that type I diabetes can develop naturally by way of an increase in MIF protein levels. For these reasons, the claimed invention is patentable over Bojunga.

The addition of Nishirira does not remedy the deficiencies of Bojunga. Nishirira describes MIF as a target molecule in multiple sclerosis. Nishirira does not teach or suggest that an agent that inhibits a macrophage migration inhibitory factor (MIF) in the mammal, wherein the agent comprises a binding site of an antibody that binds specifically to MIF, would be effective in inhibiting the progression of type 1 diabetes in a mammal having type 1 diabetes or in inhibiting the development of type 1 diabetes in a mammal at risk for type 1 diabetes.

For these reasons, the claimed invention is patentable over Bojunga in view of Nishirira. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Bojunga in view of Nishihira and U.S. Patent No. 5,530,101

Claims 28 and 33 were rejected under 35 U.S.C. §103(a) as unpatentable over Bojunga in view of Nishihira as applied to Claims 1, 3, 11 and 27 above, and further in view of U.S. Patent No. 5,530,101 ("Queen"). This rejection is respectfully traversed.

As discussed above, the claimed invention is patentable over Bojunga in view of Nishihira. The addition of Queen does not remedy the failure of Bojunga and Nishihira to render the claimed method obvious. More specifically, Queen was cited for describing the production of humanized antibodies but Queen teaches nothing regarding the use of MIF antibodies for inhibiting progress or development of type 1 diabetes as claimed.

For these reasons, the claimed invention is patentable over Bojunga, Nishihira and Queen. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

WO 01/32606 and Nishihira

Claims 1, 3, 11, 27 and 29-32 were rejected under 35 U.S.C. §103(a) as unpatentable over WO 01/32606 in view of Nishihira. This rejection is respectfully traversed.

WO 01/32606 describes compounds having MIF antagonist activity and suggest that the compounds can be used for the treatment of inflammatory disorders. However, WO 01/32606 does not provide any data showing any of its compounds are indeed useful for inhibiting the progress of type 1 diabetes in a subject having type 1 diabetes, or can be used to inhibit the development of type 1 diabetes in a subject at risk for type 1 diabetes. Furthermore, with respect to MIF antibodies, WO 01/32606 teaches that "such

biological agents, unfortunately, have certain limitations with regard to their clinical utility. Therefore there is a need in the art to discover and develop small organic molecules that function as MIF antagonists..." (WO 01/32606, page 2). This constitutes a teaching away from using an MIF antibody for therapeutic use. The addition of Nishihira does not remedy the deficiencies of the teaching of WO 01/32606. As discussed above, Nishihira describes the use of MIF as a target molecule in multiple sclerosis, not type 1 diabetes.

For these reasons, the claimed invention is patentable over WO 01/32606 and Nishihira. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

WO 01/32606 in view of Nishihira et al. and Queen

Claims 28 and 33 were rejected under 35 U.S.C. §103(a) as being unpatentable over WO 01/32606 in view of Nishihira. This rejection is respectfully traversed.

As discussed above, the claimed invention is patentable over WO 01/32606 and Nishihira. The addition of Queen does not remedy the failure of Bojunga and Nishihira to render the claimed method obvious. More specifically, Queen was cited for describing the production of humanized antibodies but Queen teaches nothing regarding the use of MIF antibodies for inhibiting progress or development of type 1 diabetes as claimed.

For these reasons, the claimed invention is patentable over Bojunga, Nishihira and Queen. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.